

ETHER AMINO ALCOHOLS

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PREFACE

The presentation of this dissertation material is purposely given in detailed form to facilitate duplication by future investigators. The description of the syntheses of compounds in a homologous series is given for all products, even though the procedure followed is basically the same for all cases.

In conformity with present usage in research reports all temperatures are of the centigrade scale, and its symbol is omitted.

The boiling points are corrected values. The thermometers used for obtaining the boiling points were calibrated against a set of thermometers standardized by the Bureau of Standards.

The manner of listing references is the customary one for technical works. Journal abbreviations are the official ones of "Chemical Abstracts".

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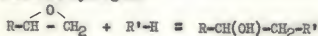
I. INTRODUCTION

The alkene oxides are reactive compounds which find unlimited use in organic syntheses. The method followed for their preparation in this work was the removal of hydrogen and halogen from 1,2-halohydrins by the use of sodium hydroxide. This method is old and well known.

A later method for the preparation of alkene oxides is that of Prileschalev (1, 2) which involves the direct introduction of an oxygen atom into the ethene group of a molecule by means of perbenzoic acid.

More recently, the lower alkene oxides have been made available in large amounts by the direct catalytic air oxidation of the corresponding olefin hydrocarbons (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15).

Alkene oxides react with compounds containing certain types of reactive hydrogen.



The class of R'-H compounds includes alcohols, amines, ammonia, water and acids.

The purpose of this investigation was to:

1. synthesize chloro-hydroxy-ethers by the use of 1,2-epoxy-3-chloro propane and alcohols;
2. synthesize epoxy-ethers by the use of chloro-hydroxy-ethers and sodium hydroxide;
3. synthesize ether-amino-alcohols from epoxy ethers and ethylene diamine.

II. DISCUSSION AND EXPERIMENTAL

A. Synthesis of 1,2-epoxy-3-chloro propane

1. Review of the Literature

1,2-epoxy-3-chloro propane, better known as epichlorohydrin is now commercially available. Shell Chemical Corporation of New Jersey sells the product in a convenient, one gallon, metallic container at a very reasonable price.

Epichlorohydrin was first synthesized in 1861 by Reboul (16) by the action of alkalis on 1,3-dichloro-2-hydroxy propane. By the same procedure, the synthesis was reported successively in 1871 by M^under and Tollens (17), in 1875 by Prevost (18), in 1877 by Claus (19) and in 1930 by Fairbourn, Gibson and Stephens (20). An alternative procedure using calcium hydroxide was reported in 1910 by Griesheim (21) and in 1932 by Braum (22).

1,3-dichloro-2-hydroxy propane is now also a commercially available product. It was synthesized by the action of hydrogen chloride on glycerol in 1853 by Berthelot (23), in 1887 by Fauconnier and Sanson (24), in 1891 by Bigot (25), and in 1918 by Smith (26). In 1912 two German Patents were issued covering its manufacture (27, 28). It was prepared in 1860 by Reboul (29) by the action of hydrogen chloride on glycerol mixed with an equal volume of acetic acid and in 1908 by Boehringer and Sons (30) by the action of hydrogen chloride or aqueous hydrochloric acid on glycerol containing one to two per cent of some organic acid as catalyst. Later, its manufacture by the action of hydrogen chloride on glycerol

containing acetic acid as a catalyst was reported in 1922 by Hill and Fischer (31) and in 1930 by Fairbourn, Gibson and Stephens (20). Finally in 1939 Dow Chemical Co. (32) was granted a patent for the production of 1,3-dichloro-2-hydroxy propane by the action of hydrogen chloride on glycerol in the presence of a water-immiscible solvent, such as dibutyl ether, and at a temperature suitable for steam distillation.

2. Experimental

In a 22-l. round bottomed flask immersed in a water bath heated to 90-95° were placed 11 kilograms of C. P. glycerol and 220 g. of acetic acid. The flask was fitted with a two-holed stopper, which carried a long tube ending in a perforated bulb reaching to the bottom of the flask and a short exit tube. The long tube was connected to a hydrogen chloride generator and the short one to the hood. Hydrogen chloride was readily prepared by dropping concentrated sulfuric acid on dry lumps of ammonium chloride. A stream of dry hydrogen chloride was passed into the mixture for a week, by the end of which time the absorption of gas had practically ceased. The product was made just alkaline to litmus with a solution of sodium carbonate. The aqueous layer was separated, extracted with benzene and incorporated into the main solution. The mixture was distilled under vacuum, the desired product being collected in the range of 71-75° at 15 mm. It was contaminated with 1,2-dichloro-3-hydroxy propane and no attempt was made to separate these isomers since both yield epichlorohydrin when treated with

sodium hydroxide. The yield of mixed dichlorohydrins corresponded to 51% of the theoretical amount.

In a 5-l. three-necked round bottomed flask, provided with an efficient mechanical stirrer, a reflux condenser and a hopper which could be closed or opened at the bottom by means of a glass bung attached to a glass rod, were placed 1900 g. (14.7 moles) of mixed glycerol dichlorohydrins and 2 liters of anhydrous ether. The flask was surrounded by an ice-water bath, and 680 g. (17 moles) of finely powdered sodium hydroxide were added through the hopper in small portions, with vigorous stirring. The water bath was allowed to reach room temperature and the mixture was stirred for eight hours. Then the ethereal solution was decanted from the solid, which was rinsed with ether. The united liquids were distilled first at atmospheric pressure to remove the excess ether and then under vacuum to yield epichlorohydrin.

B. P. : 60.5° at 100 mm.

Yield : 952 g., 10.3 moles, 70.0%

n_D^{23} : 1.4373

D_4^{23} : 1.1765

M_r_D : 20.606

B. Syntheses of Hydroxy Ethers

1. Review of the Literature

Olefin oxides react with alcohols under the influence of elevated temperatures without the use of a catalyst to produce hydroxy ethers (33). A number of catalysts have been proposed for

use in reacting an olefin oxide with an alcohol. Some investigators described the use of sulfuric acid, alkali metal alcoholates or alkali metal salts of the lower fatty acids as catalysts (34, 35). Others mentioned the use of substances like phosphoric acid, hydrochloric acid, zinc chloride, ferric chloride, caustic soda, caustic potash and organic bases (i.e., pyridine, dimethyl aniline) as catalysts in reacting olefin oxides with cellulose (36). These substances accelerate the different reactions to various degrees. The Shell Development Company (37) found very recently that stannic halides are more active and are considerably more efficient and suitable as catalysts in the reaction of an epoxy compound with an alcoholic compound.

Blanchard (38), Fournau and Ribas (39) and Fairbourne and his co-workers (40) described the reaction between epichlorohydrin and some of the alcohols. The data given for the resulting chlorohydroxy-ethers were limited mainly to those of the boiling points and these data did not agree with the results obtained in this investigation.

2. Experimental

a. Synthesis of 1-chloro-2-hydroxy-3-methoxy propane

In a 2-l., two-necked, round-bottomed flask, fitted with a stirrer and a reflux condenser, were placed nine moles (288 g., 365 cc.) of methanol and 6.7 cc. of H_2SO_4 , d. 1.84. Three moles (278 g., 235 cc.) of epichlorohydrin (1,2-epoxy-3-chloro propane) were added dropwise through the top of the reflux condenser by means

of a dropping funnel. The mixture was stirred for one hour without the application of heat and then refluxed for six hours. An excess of BaCO_3 (30 g.) was added and stirred at room temperature for several hours. The filtrate was distilled first at atmospheric pressure to remove the excess methanol, and then at 20 mm. 1-chloro-2-hydroxy-3-methoxy propane was collected at 76.5° .

B. P. : 76.5° at 20 mm.

Yield : 256 g., 2.05 moles, 68.3%

n_D^{25} : 1.4422

D_4^{25} : 1.1570

M_r : 28.49 (found) ; 28.70 (calc.)

b. Synthesis of 1-chloro-2-hydroxy-3-ethoxy propane

In a 2-l., two-necked, round-bottomed flask, fitted with a stirrer and a reflux condenser, were placed three moles (235 cc., 278 g.) of epichlorohydrin (1,2-epoxy-3-chloro propane) and six moles (350 cc., 276 g.) of absolute ethanol. Six and seven tenths cc. of H_2SO_4 (d. 1.84, assay 96.7%) (equivalent to 4 g. H_2SO_4 per mole of epichlorohydrin) were added dropwise from the top of the condenser. The mixture was refluxed for six hours, cooled and an excess of BaCO_3 (30 g.) was added. The filtrate was distilled, first at atmospheric pressure to remove the excess ethanol and then 1-chloro-2-hydroxy-3-ethoxy propane was collected at $80-82^\circ$ at 20 mm.

B. P. : $80-82^\circ$ at 20 mm. ; $105-106^\circ$ at 60 mm.

Yield : 250 g., 1.8 moles, 60.0%

n_D^{25} : 1.4370

D_4^{25} : 1.0914

M_r : 33.30 (found) ; 33.32 (calc.)

c. Synthesis of 1-chloro-2-hydroxy-3-n-propoxy propane

In a 2-l., two-necked, round-bottomed flask, fitted with a stirrer and a reflux condenser, were placed three moles (235 cc., 278 g.) of epichlorohydrin (1,2-epoxy-3-chloro propane) and six moles (350 cc., 276 g.) of propanol-1. Six and seven tenths cc. of H_2SO_4 , (d. 1.84) were added dropwise from the top of the condenser. The mixture was refluxed for six hours, cooled and an excess of BaCO_3 (30 g.) was added. The filtrate was distilled and 1-chloro-2-hydroxy-3-n-propoxy propane was collected at 97-98° at 20 mm.

B. P. : 97-98° at 20 mm.

Yield : 234 g., 1.53 moles, 51%

n_D^{25} : 1.4378

D_4^{25} : 1.0526

M_r : 38.11 (found) ; 37.94 (calc.)

d. Synthesis of 1-chloro-2-hydroxy-3-iso-propoxy propane

In a 2-l., two-necked, round-bottomed flask, fitted with a reflux condenser and a mechanical stirrer, were placed three moles (235 cc., 278 g.) of epichlorohydrin (1,2-epoxy-3-chloro propane) and six moles (459 cc., 360 g.) of propanol-2. 6.7 cc. of H_2SO_4 , d. 1.84 were added dropwise from the top of the condenser. The mixture was refluxed for six hours, cooled and excess of BaCO_3 (30 g.) was added. The filtrate was distilled and 1-chloro-2-hydroxy-3-iso-propoxy was collected at 87-87.5° at 20 mm.

B. P. : 87-87.5° at 20 mm.

Yield : 129 g., 0.845 moles, 28.2%

n_D^{25} : 1.4370

D_4^{25} : 1.0530

M_r : 37.96 (found) ; 37.94 (calc.)

e. Synthesis of 1-chloro-2-hydroxy-3-n-butoxy propane

In a 2-l., two-necked, round-bottomed flask provided with a mechanical stirrer and a reflux condenser, were placed three moles (235 cc., 278 g.) of epichlorohydrin (1,2-epoxy-3-chloro propane) and six moles (550 cc., 445 g.) of butanol-1. Six and seven tenths cc. of H_2SO_4 , (d. 1.84, assay 96.7%) (equivalent to 4 g. H_2SO_4 per mole of epichlorohydrin) were added dropwise from the top of the condenser. The mixture was refluxed for six hours, cooled and an excess of $BaCO_3$ (30 g.) was added. The filtrate was distilled, first at atmospheric pressure to remove the excess of butanol-1 and the 1-chloro-2-hydroxy-3-n-butoxy propane was collected at 110-111° at 20 mm.

B. P. : 110-111° at 20 mm.

Yield : 255 g., 1.53 moles, 57%

n_D^{25} : 1.4420

D_4^{25} : 1.0444

M_r : 42.22 (found) ; 42.56 (calc.)

f. Synthesis of 1-chloro-2-hydroxy-3-iso-butoxy propane

In a 2-l., two-necked, round-bottomed flask, fitted with a reflux condenser and a stirrer, were placed three moles (235 cc., 278 g.) of epichlorohydrin (1,2-epoxy-3-chloro propane) and nine

moles of iso-butyl alcohol (2-methyl propanol-1). Six and seven tenths cc. of H_2SO_4 (d. 1.84) were added dropwise from the top of the condenser. The mixture was refluxed for six hours, cooled and an excess of BaCO_3 (30 g.) was added. The filtrate was distilled and the 1-chloro, 2-hydroxy, 3-iso-butoxy propane was collected at 100.0-100.2° at 20 mm.

B. P. : 100.0-100.2° at 20 mm.

Yield : 188 g., 1.128 moles, 37.6%

n_D^{25} : 1.4386

D_4^{25} : 1.0313

M_r : 142.46 (found) ; 142.56 (calc.)

g. Synthesis of 1-chloro-2-hydroxy-3-n-pentoxy propane

In a 2-l., two-necked, round-bottomed flask provided with a mechanical stirrer and a reflux condenser were placed six moles (647 cc., 529 g.) of pentanol-1 and three moles (235 cc., 277 g.) of epichlorohydrin (1,2-epoxy-3-chloro propane). Six and seven tenths cc. of H_2SO_4 (d. 1.84, assay 96.7%) were added dropwise from the top of the reflux condenser. The mixture was refluxed for six hours, cooled and an excess of BaCO_3 (30 g.) was added. The filtrate was distilled, first at atmospheric pressure to remove the excess of pentanol-1 and the 1-chloro-2-hydroxy-3-n-pentoxy propane was collected at 120° at 20 mm.

B. P. : 120° at 20 mm.

Yield : 282 g., 1.56 moles, 52%

n_D^{25} : 1.4441

D_4^{25} : 1.0216

M_D : 46.98 (found) ; 47.17 (calc.)

h. Synthesis of 1-chloro-2-hydroxy-3-(3-methyl-n-butoxy)
propane

In a 2-l., two-necked, round-bottomed flask provided with a stirrer and a reflux condenser, were placed six moles (651 cc., 529 g.) of iso-amyl alcohol (3-methyl butanol-1) and three moles (235 cc., 277 g.) of epichlorohydrin (1,2-epoxy-3-chloro propane). Six and seven tenths cc. of H_2SO_4 (d. 1.84) were added dropwise from the top of the reflux condenser. The mixture was refluxed for six hours, cooled and an excess of $BaCO_3$ (30 g.) was added. The filtrate was distilled, first at atmospheric pressure to remove the excess of iso-amyl alcohol and then 1-chloro-2-hydroxy-3-(3-methyl-n-butoxy) propane was collected at 118-119° at 20 mm.

B. P. : 118-119° at 20 mm.

Yield : 249 g., 1.378 moles, 44.1%

n_D^{25} : 1.4436

D_4^{25} : 1.0223

M_D : 46.90 (found) ; 47.17 (calc.)

i. Synthesis of 1-chloro-2-hydroxy-3-(2-methyl-n-butoxy)
propane

In a 1-l., two-necked flask fitted with a reflux condenser

and a stirrer were placed one mole of epichlorohydrin (1,2-epoxy-3-chloro propane) and 2.3 moles of sec.-butyl carbinol (2-methyl butanol-1). Two and two tenths cc. of H_2SO_4 (d. 1.84) were added dropwise from the top of the reflux condenser. The mixture was refluxed six hours, cooled and an excess of $BaCO_3$ (10 g.) was added. The filtrate was distilled, first at atmospheric pressure to remove the excess 2-methyl butanol-1 and then 1-chloro-2-hydroxy-3-(2-methyl-n-butoxy) propane was collected at 114.8-115.5° at 20 mm.

B. P. : 114.8-115.5° at 20 mm.

Yield : 82 g., 0.453 moles, 45.3%

n_D^{25} : 1.4492

D_4^{25} : 1.0638

% Cl : 22.19 (found) ; 19.62 (calc.)

M_r_D : 45.56 (found) ; 47.17 (calc.)

This compound was redistilled and the constants obtained were essentially the same as those given above. The synthesis was repeated using redistilled 2-methyl butanol-1 and epichlorohydrin and still the same constants were obtained. It was observed that a colorless distillate of 1-chloro-2-hydroxy-3-(2-methyl-n-butoxy) propane, when submitted to redistillation left a dark brown residue, indicative of decomposition. The slight decomposition of the compound on distillation is a possible explanation of the high chlorine value obtained and the low observed M_r_D .

j. Synthesis of 1-chloro-2-hydroxy-3-n-hexoxy propane

In a 2-l., two-necked, round-bottomed flask provided with a stirrer and a reflux condenser, were placed three moles (235 cc., 277 g.) of epichlorohydrin (1,2-epoxy-3-chloro propane) and nine moles (919 g., 1124 cc.) of hexanol-1. Six and seven tenths cc. of H_2SO_4 , (d. 1.84), were added dropwise from the top of the reflux condenser. The mixture was refluxed for six hours, cooled and an excess of $BaCO_3$ (30 g.) was added. The filtrate was distilled and 1-chloro-2-hydroxy-3-n-hexoxy propane was collected at 133° at 20 mm.

B. P. : 133° at 20 mm.

Yield : 243 g., 1.248 moles, 41.6%

n_D^{25} : 1.4450

D_4^{25} : 1.0026

M_r : 51.67 (found) ; 51.79 (calc.)

k. The unsuccessful condensation of other alcohols with

1,2-epoxy-3-chloro propane

Sec.-butyl alcohol (butanol-2) and ter.-butyl alcohol (2-methyl-propanol-2) were treated with epichlorohydrin in the same way as described in the preceeding pages but nothing could be isolated except the original compounds

3. Discussion of Experimental Results

The molecular weights were plotted against the boiling points at 20 mm., the densities, the indices of refraction and the molecular refractions in Figures 1, 2, 3, and 4, respectively. These figures show the gradation of physical properties in correlation with molecular weight.

In the syntheses of the chloro-hydroxy-ethers the procedure followed was to mix the alcohol with epichlorohydrin and to add slowly to that mixture concentrated sulfuric acid. The procedure worked smoothly with all the primary alcohols employed, with the exception of methanol. The reaction between epichlorohydrin and methanol was too violent and the procedure had to be changed. However, if epichlorohydrin was added slowly to a mixture of methanol and sulfuric acid the reaction proceeded smoothly.

Several factors affecting the reaction between epichlorohydrin and primary alcohols catalyzed by H_2SO_4 were studied. Table I gives the relation of reflux time and yield.

TABLE I
SYNTHESIS OF 1-CHLORO-2-HYDROXY-3-n-BUTOXY PROPANE
Reaction Conditions

Ratio of butanol-1 to epichlorohydrin	G. H_2SO_4 per mole of epichlorohydrin	Reflux time, hours	Yield, per cent
2 to 1	4	2	52
2 to 1	4	6	51

The relation between the amount of sulfuric acid and the yield is given in Table II.

TABLE II
SYNTHESIS OF 1-CHLORO-2-HYDROXY-3-ETHOXY PROPANE

Reaction Conditions

Ratio of ethanol to epichlorohydrin	g. H_2SO_4 per mole of epichlorohydrin	Reflux time, hours	Yield, per cent
2 to 1	1.2	2	10.6
2 to 1	2.5	2	32.7
2 to 1	4	3.5	60.0
2 to 1	4.5	6	67

TABLE III
SYNTHESIS OF 1-CHLORO-2-HYDROXY-3-n-BUTOXY PROPANE

Reaction Conditions

Ratio of butanol-1 to epichlorohydrin	g. H_2SO_4 per mole of epichlorohydrin	Reflux time, hours	Yield, per cent
3 to 1	3	2	50.0
3 to 1	9	4	42.7

From the data presented in Table I it is evident that the per cent yield is not a function of reflux time in the range of two to six hours. By applying this conclusion to the data in Tables II and III one can see that per cent yield varies directly with the concentration of catalyst (relative to epichlorohydrin) rather than the

reflux time. The data in Table III also shows that the increase in concentration of catalyst can exceed an optimum value. This optimum appears to be 4.59 of H_2SO_4 per mole of epichlorohydrin. An excess of acid leads to secondary reactions.

Table IV shows the relation between the ratio of alcohol to epichlorohydrin and per cent yield.

TABLE IV

SYNTHESIS OF 1-CHLORO-2-HYDROXY-3-(2-METHYL-n-BUTOXY) PROPANE

Reaction Conditions

Ratio of 2-methyl butanol-1 to epichlorohydrin	g. H_2SO_4 per mole of epichlorohydrin	Reflux time, hours	Yield, per cent
2.3 to 1	4	6	45.3%
3 to 1	4	6	53.0%

The data given in Table IV indicate that by increasing only slightly the ratio of alcohol to epichlorohydrin and keeping the other factors constant the yield is increased. The yield should increase almost indefinitely by increasing the ratio of alcohol to epichlorohydrin and would be restricted only by its practicability.

Tables I through IV show that the optimum conditions in the reaction of alcohols and epichlorohydrin catalyzed by sulfuric acid are:

1. A high ratio of alcohol to epichlorohydrin
2. Four to five grams of H_2SO_4 per mole of epichlorohydrin used
3. A reflux time of two to six hours

TABLE V

SYNTHESES OF 1-CHLORO-2-HYDROXY-3-ALKOXY PROPANE

Reaction Conditions

Alkoxy radical	Ratio of alcohol to epichlorohydrin	g. H_2SO_4 per mole of epichlorohydrin	Reflux time, hours	Yield, per cent
iso-butoxy (2-methyl-n-propoxy)	3 to 1	4	6	37.6
n-butoxy	2 to 1	4	6	51.0
iso-pentoxy (3-methyl-n-butoxy)	2 to 1	4	6	44.4
n-pentoxy	2 to 1	4	6	52.0

TABLE VI

SYNTHESES OF 1-CHLORO-2-HYDROXY-3-ALKOXY PROPANE

Reaction Conditions

Alkoxy radical	Ratio of alcohol to epichlorohydrin	g. H_2SO_4 per mole of epichlorohydrin	Reflux time, hours	Yield, per cent
methoxy	3 to 1	4	6	68.3
hexoxy	3 to 1	4	6	41.6

M.W.

FIGURE 1

Boiling Points at 20 mm. vs.
Molecular Weights of Compounds
such as $\text{Cl} \cdot \text{CH}_2 \cdot \text{CH}(\text{Cl}) \cdot \text{CH}_2 \cdot \text{O} \cdot \text{R}$
where R is methyl, ethyl,
n-propyl, n-butyl, n-pentyl
and n-hexyl.

190

180

170

160

150

140

130

120

B.P. at 20 mm.

75

85

95

105

115

125

M.W.

FIGURE 2

Densities at 25° vs.
Molecular Weights of
Compounds such as
 $\text{Cl} \cdot \text{CH}_2 \cdot \text{CH}(\text{OH}) \cdot \text{CH}_2 \cdot \text{O} \cdot \text{R}$
where R is methyl, ethyl,
n-propyl, n-butyl,
n-pentyl and n-hexyl.

190

180

170

160

150

140

130

120

 D_{25}^{25}
4

0.96

1.00

1.04

1.08

1.12

1.16

M.W.

FIGURE 3

Indices of Refraction at 25°
vs. Molecular Weights of
Compounds such as
 $\text{Cl} \cdot \text{CH}_2 \cdot \text{CH}(\text{OH}) \cdot \text{CH}_2 \cdot \text{O} \cdot \text{R}$
where R is methyl, ethyl,
n-propyl, n-butyl,
n-pentyl and n-hexyl.

190

180

170

160

150

140

130

120

1.436

1.438

1.440

1.442

1.444

1.446

 n_D^{25}

M.W.

FIGURE 4

Molecular Refractions vs.
Molecular Weights of
Compounds such as
 $\text{Cl} \cdot \text{CH}_2 \cdot \text{CH}(\text{OH}) \cdot \text{CH}_2 \cdot \text{O} \cdot \text{R}$
where R is methyl, ethyl,
n-propyl, n-butyl,
n-pentyl and n-hexyl.

190

180

170

160

150

140

130

120

Mr_D

25

30

35

40

45

50

4. Summary

The reaction between epichlorohydrin and certain aliphatic alcohols catalyzed by H_2SO_4 has been investigated. Its optimum conditions have been found.

The densities, boiling points, indices of refraction and molecular refractions have been given for the ten chloro-hydroxy ethers synthesized.

Secondary and tertiary alcohols have been shown to be apparently unreactive to epichlorohydrin when H_2SO_4 is used as catalyst. Varying yields, in low amounts, have been obtained with propanol-2, the only exception found (to the preceding statement).

C. Syntheses of Epoxy Ethers

1. Review of the Literature

Epoxy ethers have been synthesized by the removal of hydrogen and halogen from halo-hydroxy-ethers. This reaction has been reported by Henry (41), Reboul (42), Nef (43), Lespieau (44), and Peratoner (45). These investigators have synthesized compounds of the type $\overset{O}{\text{CH}_2} - \text{CH} - \text{CH}_2 - \text{O} - \text{R}$ where R is methyl, ethyl and iso-pentyl (3-methyl n-butyl). Their method of synthesis has been the treatment of 1-chloro-2-hydroxy-3-alkoxy propane with concentrated solutions of alkali.

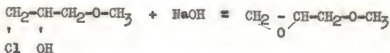
In 1930 Fournneau and Sandahl (46) reported the anesthetic properties of certain isocyclic amino alcohols of piperazine. In the syntheses of the latter series of compounds of the type $\text{R} - \text{O} - \text{CH}_2 - \text{CH}(\text{OH}) - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{CH}(\text{OH}) - \text{CH}_2 - \text{O} - \text{R}$ they pre-

pared the intermediate ethene oxides of the type $R-O-CH_2-\overset{\overset{O}{\curvearrowright}}{CH}-CH_2$. They prepared these ethene oxides by the action of concentrated NaOH on the corresponding chloro-hydroxy-ethers of the type $Cl-CH_2-CH(OH)-CH_2-O-R$. The iso-propyl, n-pentyl, and the 2-methyl-n-butyl homologues have not been reported. These are reported in this investigation with the other homologues. Some physical constants not previously noted are also listed. Fourneau and Sandahl (46) restricted the data given for the epoxy ethers reported by them to the boiling points.

In 1932 Fairbourne, Gibson and Stephens (40) reported the preparation of glycerol diethers by the action of sodium hydroxide on 1,3-dichloro-2-hydroxy propane in ethanol and found that this reaction takes place in four stages, which involve the formation and destruction of two ethene oxide rings consecutively. They investigated the conditions which govern these four separate reactions and modified them to enable the process to be stopped at any stage to afford isolation of the intermediate compounds. The rings are produced by alkali and are reopened by further alkali or by acid, although they remain stable in neutral solution. These investigators reported the synthesis of 1,2-epoxy-3-ethoxy propane by the treatment of 1-chloro-2-hydroxy-3-ethoxy propane with 27% NaOH at 80-82°.

2. Experimental

a. Synthesis of 1,2-epoxy-3-methoxy propane



In a 3-l., three-necked, round-bottomed flask, provided with an efficient mechanical stirrer, a reflux condenser and a hopper which could be opened or closed at the bottom by means of a glass bung attached to a rod, were placed two liters of ether and two moles (216 cc., 249 g.) of 1-chloro-2-hydroxy-3-methoxy propane. The flask was surrounded by an ice-water bath, and three moles (120 g.) of finely powdered sodium hydroxide were added through the hopper in small portions with vigorous stirring. The water bath was allowed to reach room temperature and the mixture was stirred for eight hours. Then 500 cc. of water were added to cause the separation of two layers which were separated in a separatory funnel. The aqueous layer was extracted with ether and the ether solutions were united and distilled, first at atmospheric pressure to remove the ethyl ether and then under vacuum so that the desired product was obtained at 53.5-53.7° at 85 mm.

B. P. : 53.5-53.7° at 85 mm.

Yield : 120 g., 1.36 moles, 68%

n_D^{25} : 1.4012

D_4^{25} : 0.9798

M_r : 21.859 (found)

b. Synthesis of 1,2-epoxy-3-ethoxy propane



In a 3-l., three-necked, round-bottomed flask, provided with a reflux condenser, an efficient mechanical stirrer and a

hopper which could be opened or closed at the bottom by means of a glass bung attached to a rod, were placed 1.5 liters of ether and 1.5 moles (191 cc., 208 g.) of 1-chloro-2-hydroxy-3-ethoxy propane. The flask was immersed in an ice-water bath, and 2.25 moles (90 g.) of finely divided NaOH were added through the hopper in small portions, with vigorous stirring. The water bath was allowed to reach room temperature and the mixture was stirred for eight hours. Then 375 cc. of water were added to cause the separation of two layers which were separated in a separatory funnel. The aqueous layer was extracted with ether and the ether solutions were united and distilled. 1,2-epoxy-3-ethoxy propane was collected at 61° at 65 mm.

B. P. : 61° at 65 mm.

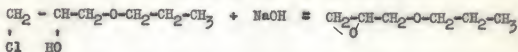
Yield : 110 g., 1.08 moles, 75%

n_D^{25} : 1.4046

D_4^{25} : 0.9430

M_r^D : 26.544

c. Synthesis of 1,2-epoxy-3-n-propoxy propane



In a 2-l., three-necked, round-bottomed flask, fitted with an efficient mechanical stirrer, a reflux condenser and a hopper which could be opened or closed at the bottom by means of a glass bung attached to a glass rod, were placed one mole (147 cc., 153 g.)

of 1-chloro-2-hydroxy-3-n-propoxy propane and one liter of ether. The flask was surrounded by an ice-water bath, and 1.5 moles (60 g.) of finely powdered sodium hydroxide were added through the hopper in small portions. The water bath was allowed to reach room temperature and the mixture was stirred vigorously for eight hours. Then 250 cc. of water were added to cause the separation of two layers which were separated in a separatory funnel. The aqueous layer was extracted with ether; the ether solutions were united and then distilled. The desired product was collected at 77.7° at 65 mm.

B. P. : 77.7° at 65 mm.

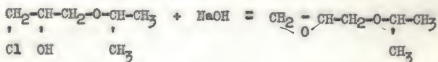
Yield : 70 g., 0.602 moles, 60.2%

n_D^{25} : 1.4103

d_4^{25} : 0.9203

M_r_D : 31.284 (found)

d. Synthesis of 1,2-epoxy-3-iso-propoxy propane



In a 2-l., three-necked, round-bottomed flask, provided with an efficient mechanical stirrer, a reflux condenser and a hopper which could be opened or closed at the bottom by means of a glass bung attached to a rod, were placed 750 cc. of ether and 0.75 moles (108 cc., 114 g.) of 1-chloro-2-hydroxy-3-iso-propoxy propane. The flask was surrounded by an ice-water bath, and 1.12 moles (45 g.)

of finely divided powdered NaOH was added through the hopper in small portions. The mixture was allowed to reach room temperature and the mixture stirred vigorously for eight hours. Then 200 cc. of water were added and the two layers formed were separated in a separatory funnel. The aqueous layer was extracted with ether; and the mixed ether solutions were distilled. 1,2-epoxy-3-isopropoxy propane was collected at 68° at 65 mm.

B. P. : 68° at 65 mm.

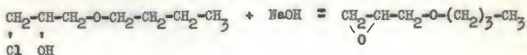
Yield : 58 g., 0.50 moles, 66.6%

n_D^{25} : 1.4068

D_4^{25} : 0.9139

M_r^D : 31.272 (found)

e. Synthesis of 1,2-epoxy-3-n-butoxy propane



In a 2-l., three-necked, round-bottomed flask, fitted with a reflux condenser, a mechanical stirrer and a hopper which could be closed or opened at the bottom by means of a glass bung attached to a glass rod, were placed one liter of ether and one mole (160 cc., 166 g.) of 1-chloro-2-hydroxy-3-n-butoxy propane. The flask was immersed in an ice-water bath and while it was being stirred vigorously, 1.5 moles (60 g.) of finely powdered NaOH were added through the hopper in small portions. The flask was removed from the water bath and the mixture stirred for eight hours at room temperature. Then 250 cc. of water were added and the layers formed were separated.

The aqueous layer was extracted with ether, and, after combination, the ether solutions were distilled. The desired product was collected at 69.7° at 20 mm.

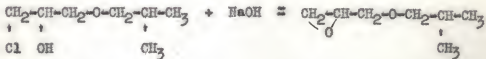
B. P. : 69.7° at 20 mm.

Yield : 114 g., 0.875 moles, 87.5%

$$n_D^{25} : 1.4150$$
$$D_L^{25} : 0.9087$$

Mr_D : 35.873 (found)

f. Synthesis of 1,2-epoxy-3-iso-butoxy propane



In a 2-l., three-necked, round-bottomed flask, fitted with a reflux condenser and an efficient mechanical stirrer, were placed one liter of ether and one mole (166 cc., 160 g.) of 1-chloro-2-hydroxy-3-iso-butoxy propane. The flask was chilled by immersing it in an ice-water bath and then 1.5 moles (60 g.) of finely powdered sodium hydroxide were added. The temperature of the water bath was allowed to reach room temperature and the mixture was vigorously stirred for eight hours. Then 250 cc. of water were added, and the two layers formed were separated. The aqueous layer was extracted with ether and, as stated previously, the ether solutions were distilled. 1,2-epoxy-3-iso-butoxy propane was collected at 65.5° at 20 mm.

B. P. : 65.5° at 20 mm.

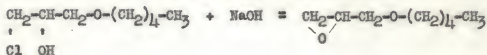
Yield : 98 g., 0.752 moles, 75.2%

n_D^{25} : 1.4112

D_4^{25} : 0.8998

M_r : 35.936 (found)

g. Synthesis of 1,2-epoxy-3-n-pentoxy propane



One liter of ether and one mole (177 cc., 181 g.) of 1-chloro-2-hydroxy-3-n-pentoxy propane were placed in a 2-l., three-necked, round-bottomed flask fitted with an efficient mechanical stirrer and a reflux condenser. The flask was surrounded by an ice-water bath and then 1.5 moles (60 g.) of finely powdered NaOH were added while stirring the mixture vigorously. The temperature of the water bath was allowed to reach room temperature and the stirring was continued for eight hours. Then 250 cc. of water were added and the two layers formed were separated. The aqueous layer was extracted with ether, the combined ether solution distilled, and the desired product collected at 86.5-86.7° at 20 mm.

B. P. : 86.5-86.7° at 20 mm.

Yield : 108 g., 0.749 moles, 74.9%

n_D^{25} : 1.4201

D_4^{25} : 0.9015

M_r : 40.484

three-necked, round-bottomed flask fitted with an efficient mechanical stirrer and a reflux condenser. The flask was surrounded by an ice-water bath. 1.7 moles (68 g.) of finely powdered NaOH were added while the mixture was stirred vigorously. The temperature of the water bath was allowed to reach room temperature and the stirring continued for eight hours. Then 250 cc. of water were added and the two layers formed were separated. The aqueous layer was extracted with ether, the combined ether solutions distilled, and the desired product collected at 76-78.5° at 20 mm.

B. P. : 76-78.5° at 20 mm.

Yield : 106 g., 0.735 moles, 64.4%

n_D^{25} : 1.4186

D_4^{25} : 0.8997

M_D : 140.443 (found)

j. Synthesis of 1,2-epoxy-3-n-hexoxy propane



In a 2-l., three-necked, round-bottomed flask, fitted with a reflux condenser and an efficient mechanical stirrer were placed one liter of ether and one mole (194 cc., 195 g.) of 1-chloro-2-hydroxy-3-n-hexoxy propane. The flask was surrounded by an ice-water bath. 1.5 moles (60 g.) of finely powdered NaOH were added with rapid agitation of the mixture. The stirring was continued for eight hours, at the end of which time the temperature of the water

bath was allowed to reach room temperature. Then 250 cc. of water were added and the resulting two layers separated. The aqueous one was extracted with ether and then the combined ether solutions were distilled, the desired product being collected at 105° at 20 mm.

B. P. : 105° at 20 mm.

Yield : 137 g., 0.865 moles, 86.5%

n_D^{25} : 1.4242

D_4^{25} : 0.8943

M_D : 45.167 (found)

3. Discussion of Experimental Results

The effect of varying amounts of NaOH in the conversion of chloro-hydroxy-ethers to epoxy ethers was investigated by Fairbourne et al (40). The amount of NaOH used in this investigation, 1.5 moles per mole of chloro-hydroxy-ether, is similar to what they used in obtaining the highest yields.

It was observed that the effectiveness of the mechanical stirrer has a direct bearing upon the yield. Table VII gives data to show this relation.

TABLE VII

SYNTHESIS OF 1,2-EPOXY-3-n-BUTOXY PROPANE
FROM 1-CHLORO-2-HYDROXY-3-n-BUTOXY PROPANE AND NaOH

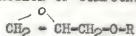
Reaction Conditions

Type of stirrer used	Yield, per cent
Ordinary stirrer	Run No. 1 = 43.8 Run No. 2 = 38.1
Modified Hershberg (47) stirrer	Run No. 1 = 81.7 Run No. 2 = 87.5

The stirrer mentioned in Table VII that was used in this investigation was built similar to that of Hershberg but instead of Nichrome wire threads, solid stainless steel blades which collapse easily were used.

The observed molecular refraction of these epoxy ethers could not be compared with the calculated values because the atomic refraction of epoxy oxygen has not been reported yet. The atomic refractions of the constituents of these epoxy ethers were added and then subtracted from the observed molecular refractions. The difference is the contribution of the epoxy oxygen to their molecular refraction. These data are given in Table VIII.

TABLE VIII
MOLECULAR REFRACTION OF COMPOUNDS OF THE TYPE:



R	Observed M_r_D	Calculated M_r_D not including the epoxy oxygen	Atomic Refraction of epoxy oxygen
methyl	21.859	20.115	1.744
ethyl	26.514	24.733	1.811
n-propyl	31.284	29.351	1.933
iso-propyl	31.272	29.351	1.921
n-butyl	35.873	33.969	1.904
iso-butyl	35.936	33.969	1.967
n-pentyl	40.484	38.587	1.897
3-methyl-n-butyl	40.501	38.587	1.914
2-methyl-n-butyl	40.443	38.587	1.856
n-hexyl	45.167	43.205	1.962

The theoretical values listed in Table VIII were calculated

from the refraction equivalents for atoms which were reported by Auwers and Eisenlohr (48) and listed by Gilman (49). These refraction equivalents are for refractive measurements made with the D line of sodium. The observed values were obtained by use of the equation of Lorenz (50) and Lorentz (51);

$$Mr_D = \frac{n^2 - 1}{n^2 + 2} \times \frac{M}{d}$$

in which d , M , and n are the density, molecular weight, and refractive index of the compound which has molecular refraction Mr_D .

The atomic refraction of epoxy oxygen given in Table VIII averages 1.890. Using this value, the observed and theoretical molecular refraction of epichlorohydrin are compared in Table IX.

TABLE IX
MOLECULAR REFRACTION OF EPICHLOROHYDRIN

n_D^{23}	: 1.4373 (Observed value)
D_4^{23}	: 1.1765 (Observed value)
Mr_D	: 20.606 (Observed value)
Mr_D	: 20.611 (Calculated value using 1.890 as the atomic refraction of epoxy oxygen)

In Table X the different refraction equivalents of oxygen linkages are listed.

TABLE X
REFRACTION EQUIVALENTS OF OXYGEN

Type of Oxygen Linkage	Atomic Refraction
Hydroxyl Oxygen	1.525 (48)
Ethereal Oxygen	1.643 (48)
Epoxy Oxygen	1.890 (This investigation)
Peroxidic Oxygen	2.19 (52)
Carbonyl Oxygen	2.211 (48)

In Figures 5, 6 and 7 the molecular weights of the compounds synthesized in this work of the type $\text{CH}_2 = \overset{\text{O}}{\text{C}} - \text{CH} - \text{CH}_2 - \text{O} - \text{R}$ were plotted against their observed densities, refractive indices and molecular refractions, respectively.

M.W.

FIGURE 5

Densities at 25° vs.
Molecular Weights of
Compounds such as

$\text{CH}_2 - \text{CH} - \text{CH}_2 - \text{O} - \text{R}$
where R is methyl, ethyl,
n-propyl, n-butyl,
n-pentyl and n-hexyl.

150

140

130

120

110

100

90

80

 D_4^{25}

0.93

0.90

0.92

0.94

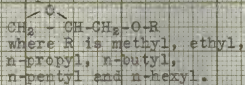
0.96

0.98

M.W.

FIGURE 6

Refractive Indices at 25°
vs. Molecular Weights of
Compounds such as



150

140

130

120

110

100

90

80

 n_D^{25}

1.400

1.405

1.410

1.415

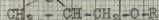
1.420

1.425

M.W.

FIGURE 7

Molecular Refractions vs.
Molecular Weights of
Compounds such as



where R is methyl, ethyl,
n-propyl, n-butyl,
n-pentyl and n-hexyl.

150

140

130

120

110

100

90

80

 M_r

20

25

30

35

40

45

4. Summary

The action of sodium hydroxide on 1-chloro-2-hydroxy-3-alkoxy propane in the production of 1,2-epoxy-3-alkoxy propane was investigated.

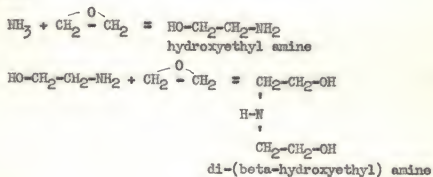
The boiling points, densities, refractive indices, and molecular refractions are given for the ten epoxy ethers synthesized.

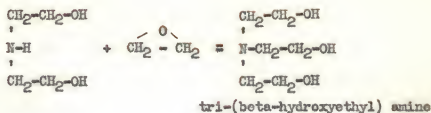
The atomic refraction of epoxy oxygen was found to be 1.890.

D. Synthesis of Ether Amino Alcohols

1. Review of the Literature

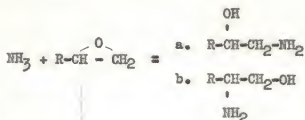
The reaction of an ethene oxide with ammonia or with an amine is of great interest in synthetic organic chemistry. It is a well known fact that aqueous solutions of ammonia may be condensed with alkene oxides to produce alkanol amines. This process was first described by Wurtz in 1860 (53). The reaction was investigated in 1897 by Knorr (54). He obtained a mixture of mono, di, and tri-hydroxy ethyl amines by treating aqueous ammonia with ethene oxide:





By the use of a large excess of ammonia, the primary amine was obtained as the main product. Advantage of this fact was taken in this investigation when the mono-alkylation of ethylene diamine was sought.

An unsymmetrically substituted ethene oxide would appear to be capable of reacting in either of two ways, depending upon which carbon retains the oxygen atom:



Krasuskii (55) found that the reaction proceeds as in case a. He formulated a rule: an asymmetrically substituted 1,2-oxide combines with ammonia to form amino-alcohols in which the hydroxyl is attached to the carbon atom which, in the original compound, was associated with the least number of hydrogen atoms.

Research on the synthesis of alkanol amines by the action of ammonia on alkene oxides is contained mainly in the patent literature (56, 57, 58, 59, 60, 61, 62). Krasuskii and Krivonos (63) in 1929 obtained 1-amino-3-methyl-2-butanol by treating $\text{CH}_3\text{-CH-CH-CH}_2\text{-NH}_2$ with 33% aqueous NH_4OH in a sealed tube for two days.

$$\begin{array}{c}
 \text{CH}_3 \quad \text{OH} \\
 | \quad | \\
 \text{CH}_3\text{-CH-CH-CH}_2\text{-NH}_2
 \end{array}$$

Processes in which aqueous solutions of aliphatic amines are condensed with alkene oxides are also well known (64) and most of these researches are contained in the patent literature (65, 66, 67, 68, 69, 70).

The manufacture of alkyl-substituted alkanol amines has been achieved by the reaction of amines with alkene oxides in processes involving the presence of very substantial quantities of water in the reaction mixture. Bodforss (71) referred to the fact that violent explosions occur even when concentrated ammonia liquid is used and stated that pure ethene oxide did not react with carefully dried ammonia gas. Whitmore (72) made the statement that diethyl amine and ethene oxide do not unite dry. Kautter (73) indicates that the reaction between alkene oxides and dry ammonia is very slow. However, very recently, Schwoegler (74) discovered that, when a body of dry diethyl amine is heated to a temperature substantially in excess of the temperature used in the aqueous method, reaction between ethene oxide and diethyl amine occurs with considerable evolution of heat.

The action of alkene oxides on di-amines has also been investigated. Krasuskii and Kosenko (75) in 1929 reported the reaction of piperazine with the oxides 2,2-dimethyl ethene and trimethyl ethene. Krasuskii and Pilyugin (76) reacted piperazine and propene oxide. All these investigators isolated only the di-substituted piperazines. Kitchen and Pollard (77) obtained the mono substituted piperazine by reacting ethene oxide and piperazine.

The reaction of ethene diamine and ethene was reported by Knorr and Brownsden (78), MacDowell (79) and by Sherlin, Berlin and Rabinovitch (80). Recently Kitchen and Pollard (17) mono-alkylated ethene diamine with propene oxide, 2-methyl propene oxide and with 2-phenylethene oxide. These reactions represent the total extent of the investigation of the reaction of alkene oxides with ethylene diamine up to the present investigation.

2. Experimental

a. Synthesis of N-(2-hydroxy-3-methoxy propyl) ethene diamine

To 10 moles (872 g. of 69.9%) of boiling ethene diamine hydrate contained in a 2-l., three-necked, round-bottomed flask, provided with a reflux condenser and a mechanical stirrer, was added dropwise through the top of the condenser one mole (90 cc., 88 g.) of 1,2-epoxy-3-methoxy propane. The mixture was refluxed and stirred for five hours. It was then distilled and the desired product was collected at 117-119° at 2 mm.

B. P. : 117-119° at 2 mm.

Yield : 123 g., 0.829 moles, 82.9%

n_D^{25} : 1.4748

D_4^{25} : 1.0446

M_D : 39.93 (found) ; 40.09 (calc.)

N, % : 18.77 (found)

H, % : 18.90 (calc. for $C_6H_{16}O_2N_2$)

b. Synthesis of N-(2-hydroxy-3-ethoxy propyl) ethene diamine

To 7.5 moles (655 g. of 69.9%) of boiling ethene diamine hydrate contained in a 1-l., three-necked, round-bottomed flask, fitted with a stirrer and a reflux condenser, was dropwise added through the top of the condenser 0.75 moles (92 cc., 86 g.) of 1,2-epoxy-3-ethoxy propane. The mixture was stirred and refluxed for five hours and then distilled. N-(2-hydroxy-3-ethoxy propyl) ethene diamine was collected at 128° at 3 mm.

B. P. : 128° at 3 mm., 126 at 2 mm.

Yield : 95 g., 0.59 moles, 78.6%

n_D^{25} : 1.4740

D_4^{25} : 1.0265

n_D : 144.41 (found) ; 144.71 (calc.)

N, % : 17.23 (found)

N, % : 17.27 (calc. for $C_7H_{18}O_2N_2$)

c. Synthesis of N-(2-hydroxy-3-n-propoxy propyl) ethene diamine

Four tenths moles (51 cc., 46 g.) of 1,2-epoxy-3-n-propoxy propane were added dropwise to four moles (348 g. of 69.9%) of boiling ethene diamine hydrate. The reaction was carried out in a 1-l., three-necked, round-bottomed flask, provided with a mechanical stirrer and a reflux condenser. The mixture was refluxed with stirring for five hours and then distilled to obtain the desired product which was collected at 130-131° at 2 mm.

B. P. : 130-131° at 2 mm.

Yield : 51 g., 0.29 moles, 72.5%

n_D^{25} : 1.4683

D_4^{25} : 0.9987

M_r : 49.08 (found) ; 49.33 (calc.)

N, % : 15.84 (found)

N, % : 15.89 (calc. for $C_8H_{20}O_2N_2$)

d. Synthesis of N-(2-hydroxy-3-iso-propoxy propyl) ethene diamine

To four moles (348 g. of 69.9%) of boiling ethene diamine hydrate contained in a 1-l., three-necked, round-bottomed flask, provided with a mechanical stirrer and a reflux condenser, 0.4 moles (51 cc., 46 g.) of 1,2-epoxy-3-iso-propoxy propane were added slowly. The mixture was stirred and refluxed for five hours and then distilled. N-(2-hydroxy-3-iso-propoxy propyl) ethene diamine was collected at 126° at 3 mm.

B. P. : 126° at 3 mm.

Yield : 54 g., 0.306 moles, 76.6%

n_D^{25} : 1.4650

D_4^{25} : 0.9875

M_r : 49.34 (found) ; 49.33 (calc.)

N, % : 15.88 (found)

N, % : 15.89 (calc. for $C_8H_{20}O_2N_2$)

e. Synthesis of N-(2-hydroxy-3-n-butoxy-propyl) ethene diamine

Seventy-five hundredths moles (108 cc., 97 g.) of 1,2-epoxy-3-n-butoxy propane were added dropwise to 7.5 moles (655 g. of 69.9%) of boiling ethene diamine hydrate. The reaction was carried on in a 2-l., three-necked, round-bottomed flask, fitted with a mechanical stirrer and a reflux condenser. The mixture was stirred and refluxed for five hours and then distilled. N-(2-hydroxy-3-n-butoxy propyl) ethene diamine was collected at 134-135° at 2 mm.

B. P. : 134-135° at 2 mm.

Yield : 115 g., 0.604 moles, 80.5%

n_D^{25} : 1.4654

D_4^{25} : 0.9775

M_r : 53.85 (found) ; 53.95 (calc.)

N, % : 14.62 (found)

N, % : 14.72 (calc. for $C_9H_{22}O_2N_2$)

f. Synthesis of N-(2-hydroxy-3-iso-butoxy propyl) ethene diamine

To six moles (522 g. of 69.9%) of boiling ethene diamine hydrate contained in a 1-l., three-necked, round-bottomed flask, were added dropwise 0.6 moles (87 cc., 78 g.) of 1,2-epoxy-3-iso-butoxy propane. The flask was provided with a reflux condenser and a mechanical stirrer. The mixture was stirred and refluxed for five hours and then distilled. The desired product was collected at 133° at 3 mm.

B. P. : 133° at 3 mm.

Yield : 87 g., 0.457 moles, 76.3%

n_D^{25} : 1.4627

D_4^{25} : 0.9694

M_D : 53.99 (found) ; 53.95 (calc.)

N, % : 14.66 (found)

N, % : 14.72 (calc. for $C_9H_{22}O_2N_2$)

g. Synthesis of N-(2-hydroxy-3-n-pentoxo propyl) ethene diamine

Five tenths moles (80 cc., 72 g.) of 1,2-epoxy-3-n-pentoxo propane were added dropwise to five moles (436 g. of 69.9%) of boiling ethene diamine hydrate contained in a 1-l., three-necked, round-bottomed flask. The latter was fitted with a reflux condenser and a mechanical stirrer. The mixture was refluxed and stirred for five hours and then distilled. The desired product was collected at 149-150° at 2 mm.

B. P. : 149-150° at 2 mm.

Yield : 85 g., 0.416 moles, 83.2%

n_D^{25} : 1.4645

D_4^{25} : 0.9660

M_D : 58.41 (found) ; 58.56 (calc.)

N, % : 13.65 (found)

N, % : 13.71 (calc. for $C_{10}H_{24}O_2N_2$)

h. Synthesis of N-[2-hydroxy-3-(3-methyl-n-butoxy) propyl]
ethene diamine

To five moles (436 g. of 69.9%) of boiling ethene diamine hydrate contained in a 1-l., three-necked, round-bottomed flask, provided with a reflux condenser and a mechanical stirrer, were added dropwise through the top of the condenser 0.5 moles (80 cc., 72 g.) of 1,2-epoxy 3-(3-methyl-n-butoxy) propane. The mixture was refluxed and stirred for five hours and then distilled. The desired product was collected at 145.7° at 2 mm.

B. P. : 145.7° at 2 mm.

Yield : 86 g., 0.42 moles, 84%

n_D^{25} : 1.4641

D_4^{25} : 0.9635

M_r : 58.52 (found) ; 58.56 (calc.)

N, % : 13.66 (found)

N, % : 13.71 (calc. for $C_{10}H_{24}O_2N_2$)

i. Synthesis of N-[2-hydroxy-3-(2-methyl-n-butoxy) propyl]
ethene diamine

Five tenths moles (80 cc., 72 g.) of 1,2-epoxy-3-(2-methyl-n-butoxy) propane were added dropwise to five moles (435 g. of 69.9%) of boiling ethene diamine hydrate. The reaction was conducted in a 1-l., three-necked, round-bottomed flask, provided with a reflux condenser and a mechanical stirrer. The mixture was stirred and re-fluxed for a period of five hours and then distilled. The desired product was obtained at 142° at 2 mm.

B. P. : 142° at 2 mm. ; 143.7° at 3 mm.

Yield : 79 g., 0.386 moles, 77.2%

n_D^{25} : 1.4648

D_L^{25} : 0.9630

M_r : 58.61 (found) ; 58.56 (calc.)

N, % : 13.56 (found)

N, % : 13.71 (calc. for $C_{10}H_{24}O_2N_2$)

j. Synthesis of N-(2-hydroxy-3-n-hexoxy-propyl) ethene
diamine

To 7.45 moles (648 g. of 69.9%) of boiling ethene diamine hydrate contained in a 1-l., three-necked, round-bottomed flask, provided with a mechanical stirrer and a reflux condenser were added dropwise through the top of the condenser, 0.745 moles (132 cc., 118 g.) of 1,2-epoxy-3-n-hexoxy propane. The mixture was refluxed and stirred for five hours and then distilled. N-(2-hydroxy-3-n-hexoxy-propyl) ethene diamine was collected at 158° at 2 mm.

B. P. : $155.5 - 156^{\circ}$ at 1 mm.; 158° at 2 mm.; 160° at 3 mm.

Yield : 128 g., 0.587 moles, 78.7%

n_D^{25} : 1.4650

D_L^{25} : 0.9549

M_r : 63.19 (found) ; 63.18 (calc.)

N, % : 12.74 (found)

N, % : 12.85 (calc. for $C_{11}H_{26}O_2N_2$)

3. Discussion of Experimental Results

The alkylation of ethene diamine with an epoxy ether has not been reported. However, the alkylation of ammonia and amines with alkylene oxides is a well known reaction. It was reported by Knorr (81) that the primary amine was the main product obtained when a large excess of ammonia was reacted with ethene oxide. Kitchen and Pollard (77) showed that the mono-alkylation of piperazine with ethene oxide and of ethene diamine with propene oxide, 2-methyl propene oxide and with 2-phenylethene oxide was accomplished when a large excess of the amine involved was used. With this established fact, the process followed in this investigation for the mono-alkylation of ethylene diamine with an epoxy ether was the use of a high mole ratio of amine to oxide. The lowest ratio at any time was ten to one because one molar equivalent of the oxide was added dropwise to ten molar equivalents of the amine. The reaction was carried on at the highest possible temperature, i.e. boiling ethene diamine hydrate, in order that the reaction occur as soon as the oxide came in contact with the amine and an excess of the former never exist. This was done to limit to a minimum secondary reactions such as the di-, tri-, and tetra-alkylation of ethene diamine which are all possible.

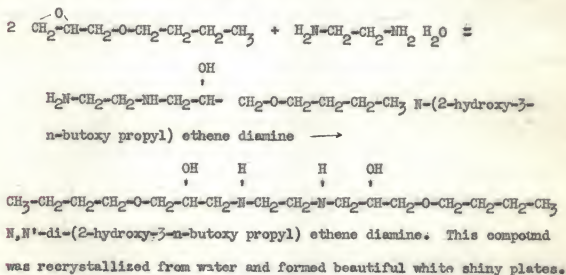
In one case the mole ratio of amine to oxide was decreased and the yield of the mono-alkylated ethene diamine was substantially decreased and a small amount of the di-substituted compound isolated. These data are given in Table XI.

TABLE XI

REACTION OF ETHENE DIAMINE HYDRATE AND 1,2-EPOXY-
3-n-BUTOXY PROPANE

Mole ratio of amine to oxide	Yield of mono- substituted ethylene diamine, per cent	Yield of di- substituted ethylene diamine, per cent
2 to 1	44.3	3.7
4 to 1	56.0	2.2
10 to 1	80.5	0

The disubstituted ethene diamine compound mentioned in
Table XI is N,N'-di-(2-hydroxy-3-n-butoxy propyl) ethene diamine:



M. P. : 121 - 122°

N, % : 8.82 (found)

N, % : 8.74 (calc. for $C_{16}H_{26}O_4N_2$)

Mol.Wt.: 323.2 (found by Rast's (82) camphor method)

Mol.Wt.: 320.4 (calc.)

Mono-naphthyl isocyanate derivative : (Recrystallized from benzene and heptane)

M. P. : 138 - 140°

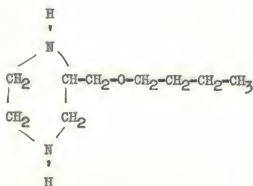
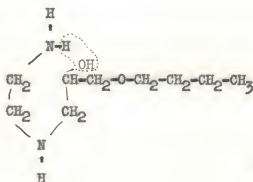
N, % : 8.63 (found)

N, % : 8.58 (calc. for $C_{27}H_{43}O_5N_3$)

Mol.Wt.: 496.4 (found by Rast's (82) camphor method)

Mol.Wt.: 489.6 (calc.)

The cyclo-dehydration of N-(2-hydroxy-3-n-butoxy propyl) ethene diamine for the production of substituted piperazine was attempted:



No success was obtained in this attempt. The procedure followed was refluxing the mono-substituted ethene diamine in the presence of a high boiling and inert solvent such as diethyl carbitol, and Raney (83) nickel as catalyst. Kitchen and Pollard (84) and Goulding and Pollard (85) have used this catalyst successfully in the cyclo-dehydration of certain amino-alcohols. In this investigation, it was found that no reaction took place or the original ether-amino-alcohol decomposed when submitted to more drastic treatments such as the subjection of the reaction mixture to pressure. In one instance a trace of a hygroscopic compound was isolated when 30 parts of N-(2-hydroxy-3-n-butoxy propyl) ethene diamine were refluxed with 30 parts of diethyl carbitol and 1 part of Raney nickel followed by distillation, this compound was collected at 82-83° at 65 mm.

B. P. : 82-83° at 65 mm.

F. P. : 48.6-49°

On analysis it showed 23.8% N, and eight days after standing in a dessicator it showed only 5.5% N. Due to the instability of this compound, its structure could not be determined.

In Figures 8, 9, 10, and 11 the molecular weights of these new ether amino alcohols of the type $H_2N-CH_2-CH_2-NH-CH_2-CH(OH)-CH_2-O-R$ have been plotted against their observed boiling points, densities, refractive indices and molecular refractions.

M.W.

FIGURE 3

Boiling Points at 2 mm.
vs. Molecular Weights of
Compounds such as
 $H_2N-CH_2-CH_2-NH-CH_2-CH(OH)-CH_2-O-R$
where R is methyl, ethyl,
n-propyl, n-butyl, n-pentyl
and n-hexyl.

210

200

190

180

170

160

150

140

B.P. at 2 mm.

110

120

130

140

150

160°

M.W.

FIGURE 9

Densities at 25° vs.
Molecular Weights of
Compounds such as
 $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{R}$
where R is methyl, ethyl,
n-propyl, n-butyl,
n-pentyl and n-hexyl.

210

200

190

180

170

160

150

140

 D_4^{25}

0.94

0.96

0.98

1.00

1.02

1.04

M.W.

210

200

190

180

170

160

150

140

1.464

1.466

1.468

1.470

1.472

1.474

FIGURE 10

Refractive Indices at 25°
vs. Molecular Weights of
Compounds such as
 $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{R}$
where R is methyl, ethyl,
n-propyl, n-butyl,
n-pentyl and n-hexyl.

 n_D^{25}

M.W.

FIGURE 11

Molecular Refractions vs.
Molecular Weights of
Compounds such as
 $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{R}$
where R is methyl, ethyl,
n-propyl, n-butyl,
n-pentyl and n-hexyl.

190

180

170

160

150

140

 Mr_D

35

40

45

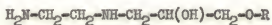
50

55

60

4. Summary

The mono-alkylation of ethene diamine with epoxy ethers in the production of ether amino alcohols of the type



where R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, n-pentyl, 3-methyl-n-butyl, 2-methyl-n-butyl, and n-hexyl has been accomplished. The boiling points, yields obtained, refractive indices, densities, molecular refraction and nitrogen contents are given for these ten new compounds.

III. Organo Arsenicals

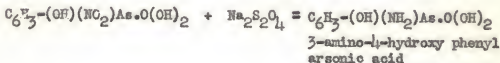
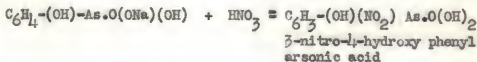
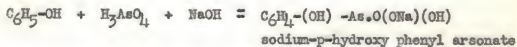
A. Introduction

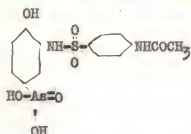
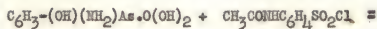
This part of this investigation was originally intended to be the main one. Its goal was the synthesis of compounds of the type of Mapharsen (3-amino-4-hydroxy-phenyl arsenoxide) and Arsphenamine (3,3'-diamino-4,4'-di-hydroxy arsene benzene) containing sulfanilamido radicals. At the time this project was started, a search of the recorded literature was made and no compounds were found that were of the nature of those intended to be made. However, investigation in this field was abandoned after several months of work, as soon as a copy of U. S. Patent No. 2,409,291 (86), obtained at the earliest possible date, revealed that duplication had occurred.

A short resume of the work done in this field will be given without trying to enter in the discussion of the lengthy literature of organo arsenicals and sulfanilamide and its many derivatives.

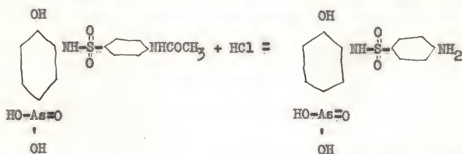
B. Experimental

The goal of this project was the accomplishment of the following syntheses:

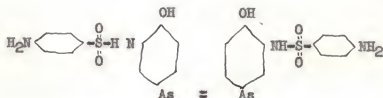
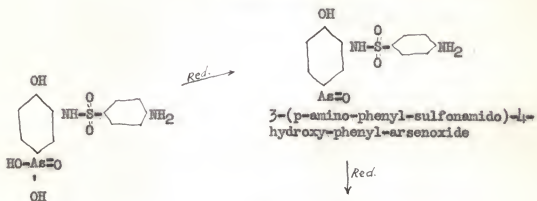




3-(p-acetamino-phenyl-sulfonamido)-4-hydroxy phenyl arsonic acid.

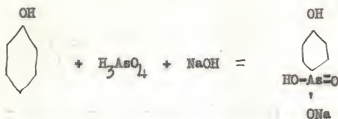


3-(p-amino-phenyl-sulfonamido)-4-hydroxy phenyl arsonic acid



3,3'-di(p-amino-phenyl-sulfonamido)-4,4'-dihydroxy-arsenobenzene

1. Synthesis of sodium p-hydroxy-phenyl arsonate

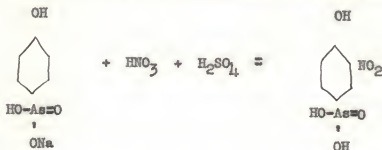


Six Hundred g. of syrupy orthoarsenic acid (95) were added to 300 g. of phenol suspended in 500 g. of o-di-chlorobenzene contained in a 2-l., two-necked, round-bottomed flask provided with an efficient mechanical stirrer and a still head. The flask was set in a mineral oil bath which was heated to 155-160° and the stirrer was run at high speed rate. Water, o-di-chlorobenzene and a small amount of phenol were distilled out. The distillation was continued until 58 cc. of water were collected. The still head was then set on total reflux and the reaction was continued for five hours. The mixture was poured into three liters of water in a crock and made slightly alkaline to litmus by the gradual addition of barium hydroxide. The barium arsenate was removed by filtration. The o-di-chlorobenzene layer was separated from the mother liquor. The latter was treated with sulfuric acid until free from sulfate and barium ions, the filtrate was evaporated to about two liters, neutralized to litmus with sodium hydroxide and filtered. The filtrate was evaporated until crystallization was well under way, and then treated with twice its volume of ethanol. The mixture was allowed to stand overnight, the sodium p-hydroxy phenyl arsonate filtered, washed with alcohol

and dried in an oven at 75°. The yield consisted of 280 grams of 80% pure salt corresponding to 29.3%. The direct arsonation of phenol as just described was reported with slight variations by Conant (87), Jacobs and Heidelberger (88), and by Christiansen and Norton (89). A German patent (90) was granted on the process.

Sodium p-hydroxy phenyl arsonate synthesized as described above is contaminated with varying amounts of sodium sulfate. There is no simple criterion of purity, such as a melting point determination. Since an exact amount must be taken for the subsequent step, i.e. nitration, this difficulty is significant. However, Conant (87) has devised a method of analysis fairly accurate and rapid to circumvent this difficulty. The method resembles the bromine titration of phenol. About 0.1 g. of the substance dried at 100° is weighed into a glass-stoppered flask and dissolved in a little water. Fifteen cc. of an approximately normal solution of bromine are added. The flask is stoppered and shaken several minutes. An excess of potassium iodide is now added. The flask is shaken again and the solution is titrated with 0.1 N. $\text{Na}_2\text{S}_2\text{O}_3$. The bromine solution is compared with the thiosulfate before each determination.

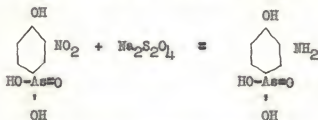
2. Synthesis of 3-nitro-4-hydroxy-phenyl arsonic acid



Two hundred and seventy-five g. of crude sodium p-hydroxy phenyl arsonate containing 0.75 moles of the organic salt were slowly stirred into 500 cc. of H_2SO_4 , (d. 1.84), kept at 0°. The reaction was conducted in a 2-l., two-necked, round-bottomed flask, provided with a reflux condenser and a stirrer. The nitrating mixture, consisting of 0.75 moles (48 cc.) of HNO_3 (d. 1.42, assay 70.5%) and 48 cc. of H_2SO_4 (d. 1.84) was introduced dropwise from the top of the condenser, then the temperature was allowed to rise slowly to 15°. It was kept at this temperature while being stirred for four hours. The mixture was then poured into 2.5 liters of water and placed in the refrigerator for two days. The nitro-hydroxy arsonic acid was filtered, recrystallized from water and air dried. The yield was 0.5 moles (131.5 g.) which corresponded to 66% of the theoretical.

The synthesis of 3-nitro-4-hydroxy phenyl arsonic acid by the nitration of sodium p-hydroxy phenyl arsonate has been reported by Benda and Berthelm (91) and by Conant (87).

3. Synthesis of 3-amino-4-hydroxy-phenyl arsonic acid

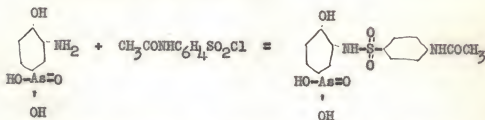


Twenty g. (0.076 moles) of 3-nitro-4-hydroxy-phenyl arsonic acid were suspended in 50 cc. of water in a 1-l., round-bottomed flask and were dissolved by adding 15 cc. of 40% NaOH solution. A

solution of 40 g. of magnesium chloride crystals in 300 cc. of water was added, and the whole was cooled to 0°. Then it was reduced by the gradual addition of 80 g. of sodium hydrosulfite with continuous mechanical stirring. After stirring for two hours and keeping the temperature at 0°, a white precipitate of the amino-hydroxy arsonic acid appeared. This was filtered from the liquid, washed with cold water, methanol and ether. 3-amino-4-hydroxy arsonic acid is oxidized by air when not pure. Its recrystallization must be done immediately after its isolation. It is recrystallized from water in a nitrogen atmosphere. After it has been purified the compound is stable to air oxidation. In this investigation, the purification was carried out in a manner similar to that of the one by Raiziss and Fisher (92) which consisted of recrystallization of the compound from water in an atmosphere of nitrogen. It was found that a large portion of the compound was lost in this step. So it was decided that the crude amino compound be used for the next step immediately after it was isolated. Excellent results were obtained when this procedure was followed.

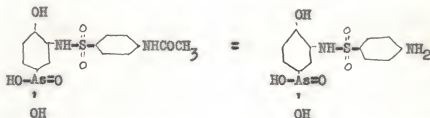
Sodium hydrosulfite was used as the reducing agent in the conversion of 3-nitro-4-hydroxy-phenyl arsonic acid into the corresponding amino compound by Raiziss and Gavron (93), and by Fargher (94). The use of sodium amalgam as the reducing agent was reported by Ehrlich and Bertheim(95). Jacobs, Heidelberger and Rolf (96) used ferrous sulfate to accomplish the reduction and finally Mouneyrat (97) did it by electrolytic methods.

4. Synthesis of 3-(p-acetamino-phenyl-sulfonamido)-4-hydroxy phenyl arsonic acid



The crude, air-dried, reaction product obtained by the reduction of 50 g. of 3-nitro-4-hydroxy phenyl arsonic acid with sodium hydro-sulfite was added at once to 200 cc. of water containing 12 g. of sodium carbonate and 70 g. of p-acetaminobenzene sulfonyl chloride (synthesized by the action of chlorosulfonic acid on acetanilide; Org. Syn. Coll. Vol. 1, P.8). The mixture was stirred for 30 minutes at room temperature. Three successive portions of normal sodium carbonate (300 cc. each) were then added at 30 minute intervals with continuous stirring. The unreacted sulfonyl chloride was filtered out. The filtrate was cooled to 0° and, while being stirred vigorously, acidified with normal HCl. The solution turned pink and 3-(p-acetamino-phenyl-sulfonamido), 4-hydroxy phenyl arsonic acid di-hydrate separated out. It was recrystallized from an alcohol-benzene mixture. It was insoluble in water, soluble in alcohol and in dilute alkali. It gave a negative Bratton-Marshall (98) test for the presence of primary aromatic amines. It showed an arsenic content of 16.0% compared to a calculated value of 16.06%.

5. Synthesis of 3-(p-amino-phenyl-sulfonamido)-4-hydroxy
phenyl arsonic acid



The hydrolysis of the acetylated compound was attempted by using an alkaline hydrolysis, an acid hydrolysis, and simple reflux with water. The alkaline hydrolysis yielded an unworkable tarry material; the acid hydrolysis de-arsenified the compound yielding sulfanilic acid; and the hydrolysis with water alone gave only a trace of the free amine compound. Ten g. of the acetylated compound was suspended in 200 cc. of water and refluxed for 60 hours. On cooling the free amino compound separated. It was recrystallized from water. It darkened at 230° but at 300° it was still unmelted. It was insoluble in alcohol and gave a positive Bratton-Marshall (98) test. On analysis it showed an arsenic content of 17.42% and a nitrogen content of 6.47% compared to a theoretical of 17.60% arsenic and 6.60% nitrogen for 3-(p-amino-phenyl-sulfonamido), 4-hydroxy phenyl arsonic acid di-hydrate.

The troubles encountered in the hydrolysis of the acetylated compound were great and new derivatives such as the carbobenzoxy were being considered when the investigation in this field had to be abandoned.

IV. SUMMARY

The condensation of 1,2-epoxy-3-chloro propane with certain alcohols (methanol, ethanol, propanol-1, propanol-2, butanol-1, 2-methyl-propanol-1, pentanol-1, 3-methyl-butanol-1, 2-methyl-butanol-1 and hexanol-1) catalyzed by sulfuric acid was investigated.

The syntheses of epoxy-ethers of the type $\text{CH}_2 - \overset{\text{O}}{\text{CH}} - \text{CH}_2 - \text{O} - \text{R}$ was accomplished by the action of sodium hydroxide on the corresponding chloro-hydroxy-ethers of the type $\text{Cl} - \text{CH}_2 - \text{CH}(\text{OH}) - \text{CH}_2 - \text{O} - \text{R}$.

Ten new ether-amino-alcohols of the type $\text{H}_2\text{N} - \text{CH}_2 - \text{CH}_2 - \text{NH} - \text{CH}_2 - \text{CH}(\text{OH}) - \text{CH}_2 - \text{O} - \text{R}$ were obtained by the mono-alkylation of ethene diamine hydrate with epoxy-ethers of the type $\text{CH}_2 - \overset{\text{O}}{\text{CH}} - \text{CH}_2 - \text{O} - \text{R}$ where R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, 2-methyl-n-propyl, n-pentyl, 3-methyl-n-butyl, 2-methyl-n-butyl and n-hexyl.

3-(p-amino-phenyl-sulfonamido)-4-hydroxy phenyl arsonic acid was prepared by the condensation of 3-amino-4-hydroxy-phenyl arsonic acid with p-acetamino benzene sulfonyl chloride followed by hydrolysis.

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VII. BIOGRAPHICAL ITEMS

Hector Flores-Gallardo was born in Naguabo, Puerto Rico, on November 28, 1918. He pursued his undergraduate studies at the University of Puerto Rico and was awarded the degree of Bachelor of Science in May, 1939. In April, 1940 he passed the examinations given by the Board of Examiners of Chemists of the Government of Puerto Rico and was authorized to pursue the practice of chemistry in that island. From June, 1939 to July, 1941 he was the director of the distillery department of the Butanol-Acetone Plant of Central Lafayette at Arroyo, Puerto Rico.

Mr. Flores-Gallardo entered the Graduate School of the University of Florida in September 1941. He received the Master of Science degree in May 1942. He continued his Graduate study until he entered the U. S. Army in January 1944. He was honorably discharged from the U. S. Army in January, 1946 and resumed his Graduate studies in Chemistry at the University of Florida.

VIII. COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Date July 25, 1947

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